Biology of Mucosal Pain

Christine Miaskowski

Pain is experienced when injury to mucosal tissues occurs. Although the neurobiology of mucosal pain has not been fully elucidated, research has demonstrated that the oral mucosa contains primary afferent nociceptors that respond to thermal, mechanical, and chemical stimuli. Inflammation occurs during the initial phase of mucosal injury caused by stomatotoxic chemotherapy or radiation therapy. This article reviews the mechanisms that underlie acute pain in inflamed cutaneous tissue and summarizes the major mediators that activate and sensitize primary afferent nociceptors. Recommendations for future research to elucidate the neurobiology of mucosal pain throughout the gastrointestinal tract are presented. [J Natl Cancer Inst Monogr 2001;29:37–40.]

Pain is a major clinical problem for most patients who sustain mucosal injury from cancer chemotherapy or radiation therapy. Little information is available, however, on the mechanisms of pain associated with mucosal injury in patients with cancer. Therefore, much of the information provided in this article on the mechanisms of pain associated with mucosal injury is extrapolated from research studies that have evaluated pain mechanisms in the presence of inflammation in cutaneous tissues.

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (1). Although it is recognized that pain associated with mucosal injury in patients with cancer includes an emotional component that is related to the cancer diagnosis and the stress of the treatment, this article focuses on the sensory portion of the pain experience and describes the biochemical changes that occur in response to tissue injury and that result in the sensation of pain.

Types of Cancer Pain

Cancer pain is categorized as somatic, visceral, or neurogenic in origin (2). Somatic pain occurs as a result of the activation of nociceptors in cutaneous and deep tissues. Somatic pain is typically constant and well localized and is frequently described as aching, throbbing, or gnawing. Both bone metastasis and mucosal injury produce somatic pain.

Visceral pain originates from injury to sympathetically innervated organs. Mechanisms of visceral pain include necrosis, ischemia of visceral muscle, serosal or mucosal irritation by algic substances, or abnormal distention or contraction of smooth muscle walls within a hollow viscus. The pain is characterized as either dull, deep, and aching or paroxysmal and colicky (2).

Neuropathic pain refers to pain syndromes that occur as a result of nerve injury. Neuropathic pain can occur following surgery or radiation therapy. In addition, certain chemotherapeutic agents (e.g., Taxol, vincristine, vinblastine, and cisplatin) can produce neuropathic pain. This pain is characterized by burning, tingling, and numbing sensations (2).

Pain associated with mucosal injury in the oral cavity can be categorized as somatic (2). Pain associated with mucosal injury in the upper and lower gastrointestinal tract may exhibit the characteristics of visceral pain (2). Research studies are needed, however, that describe the multiple dimensions and more accurately characterize the types of pain that occur with mucosal injury in the oral cavity as well as in the upper and lower gastrointestinal tract. One possible method of accomplishing this would be to have patients describe their pain using the sensory and affective descriptors from the McGill Pain Questionnaire (1). Categorization of the sensory and affective dimensions of the pain associated with mucosal injury would demonstrate which pain dimension is more relevant to patients over time and would also allow researchers to determine which pain descriptors are associated with different types of cancer treatment or with different locations in the gastrointestinal tract. Characterization of this pain as somatic, visceral, or neuropathic is useful clinically and would be aided by patients’ assessment of these dimensions of their pain.

Epidemiology of Pain Associated With Mucosal Injury

Pain associated with mucosal injury can occur during chemotherapy, radiation therapy, or bone marrow transplantation. Oral pain associated with stomatotoxic chemotherapy is prevalent in from 40% to 70% of all patients (4). In patients who receive radiation therapy to the head and neck region, as many as 100% will experience pain that increases in severity during the course of treatment and persists after the treatment (5–8). Several studies (9–11) have documented that oral pain associated with bone marrow transplantation is prevalent in from 60% to 85% of all patients. More detailed studies are needed, however, to describe the patterns of oral and rectal pain associated with cancer treatment and to determine whether pain persists following treatment.

Concerning primary or adjuvant chemotherapy, detailed longitudinal studies are needed to determine the patterns of pain intensity associated with various chemotherapy regimens. Information is needed on the intensity and characteristics of pain associated with the initial course of chemotherapy as well as with subsequent courses of chemotherapy.

Radiation therapy to the head and neck region is associated with mucosal injury and pain. The temporal development of radiation-induced pain and the effects of pain on the activities of daily living were evaluated in a study of 14 patients (12) who underwent radiation therapy for head and neck cancer. All patients developed painful mucositis that began during the second...
or third week of radiation therapy. Despite the use of analgesics and anesthetics, the pain experienced by patients was rated as moderate or severe on 37% of the treatment days and was noted to be constant or present throughout most of the day on 58% of the treatment days. Eating and sleep disturbances associated with pain occurred on 55% and 34% of the treatment days, respectively.

Patients who undergo bone marrow transplantation receive high doses of chemotherapy with or without radiation therapy. Patterns of mucositis and pain were evaluated in a study of 47 patients who underwent bone marrow transplantation with high-dose chemotherapy without total-body irradiation (9). The patients’ oral cavities were assessed daily, from 9 days before transplant through 21 days after transplant. The patients’ oral cavities were assessed for the extent and severity of mucositis; patients reported oral pain by using the short form of the McGill Pain Questionnaire (13). Eighty-nine percent of the patients developed oral mucositis, which began an average of 3 days after transplant, lasted 9.5 days, and was resolved by 12.6 days after transplant. Eighty-six percent of the patients reported oral pain that began an average of 4.5 days after transplant, lasted 6.4 days, and was resolved by 11 days after transplant.

The epidemiology of pain associated with mucosal injury in the oral cavity and in the upper and lower gastrointestinal tract needs to be examined in more detail. Longitudinal studies are needed that evaluate the characteristics, location, and severity of pain associated with all somatotoxic cancer treatment modalities. Also, consideration needs to be given to the scales that are used to measure the severity of the pain that occurs with mucosal injury. Traditional numeric rating scales ranging from 0 (no pain) to 10 (worst pain imaginable) may not be appropriate when evaluating a pain problem that escalates over the course of treatment and for which patients have no prior concept. In these cases, the risk is that the scale’s ceiling will be approached well before the highest level of pain is reached unless patients are told that they can use a number higher than 10 if their pain exceeds their previous threshold of “worst pain imaginable.” In addition, studies of therapies that are directed at preventing or treating mucosal injury associated with cancer treatment should measure multiple dimensions of the pain experience, including pain intensity and pain relief (i.e., from 0 = no relief to 100 = complete relief) as part of any outcome evaluation of the effectiveness of these therapies.

BIOLOGY OF MUCOSAL PAIN

Neuroanatomic Considerations

Peripheral nerves that respond to noxious stimuli are best characterized in the skin because there they are more accessible for electrophysiologic studies. Those nerves that respond preferentially to noxious stimuli are termed nociceptors. Nociceptors are classified on the basis of the following criteria: conduction velocity, specific response characteristics, presence or absence of a myelin sheath, and modalities of stimulation that evoke a response. On the basis of these criteria, two main classes of cutaneous nociceptors have been characterized: 1) Aδ high-threshold mechanoreceptors are myelinated nociceptors that respond with higher discharge frequencies and provide more discriminative information to the central nervous system, and 2) C-polymodal nociceptors are unmyelinated fibers that provide a more diffuse response to noxious stimulation (14,15).

Only one study (16) was found that described the characteristics of mucosal nociceptors in the oral cavity of the rat. This in vitro, jaw-nerve preparation of the adult rat evaluated nociceptors in the oral mucosa of the lower jaw by recording activities from single fibers in the lingual nerve. Responses were recorded from a total of 124 single fibers. Fifty-seven percent of the fibers were classified as non-nociceptive. The remaining 67 fibers were characterized by using mechanical (i.e., calibrated von Frey hairs), heat (up to 50 °C), and chemical (i.e., bradykinin) stimuli.

Four types of oral mucosal nociceptors were found: 11 Aδ high-threshold mechanoreceptors, seven Aδ mechanoheat receptors, 21 Aδ polymodal nociceptors, and 28 C-polymodal nociceptors. The majority of the nociceptors in the rat’s oral mucosa were of the polymodal type. The major characteristics of the nociceptors in the oral mucosa are summarized in Table 1. The fact that the oral mucosa consists mainly of polymodal nociceptors seems to make it functionally suitable for detecting the characteristics of ingested food or drink, which provide various chemical, mechanical, and thermal stimuli to the oral mucosa (16). However, because of the paucity of the research in this area, additional studies are warranted to characterize the various types of nociceptors in the oral mucosa of different animal species. In addition, the nociceptors in the upper and lower gastrointestinal tract need to be enumerated and characterized.

Mechanistic Considerations

The biology of mucosal pain can be explained by using a model of tissue injury (Fig. 1). Injury to the oral mucosa in patients with cancer occurs as a result of the systemic administration of stomatotoxic chemotherapy or the administration of ionizing radiation to the head and neck region or to the upper or lower gastrointestinal tract (17). While the biology of mucosal pain has not been characterized, the mechanisms of cutaneous pain associated with tissue damage and inflammation are well described [for review, see (15)] and are summarized here.

Tissue injury initiates the process of inflammation, characterized by pain, heat, redness, swelling, and loss of function. Pain occurs because primaryafferent nociceptors are activated by or become sensitized to noxious stimuli. During inflammation, nociceptors exhibit a lower threshold for stimulation-induced pain or an increased responsiveness to noxious stimuli. The clinical correlate of sensitization is hyperalgesia, when the patient reports “tenderness” at the site of inflammation.

Table 1. Characteristics of nociceptors in the oral mucosa of the rat*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Description</th>
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<td>• The receptive field of the polymodal nociceptors in the oral mucosa is statistically significantly larger than that of the Aδ high-threshold mechanoreceptors or the Aδ mechanoheat receptors.</td>
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<tr>
<td>• The C-polymodal nociceptor in the oral mucosa has the largest receptive field.</td>
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<td>• No statistically significant differences were found in the threshold for von Frey stimulation among the four types of nociceptors in the oral mucosa.</td>
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<td>• The heat threshold of Aδ polymodal nociceptors was statistically significantly lower than that of the other three types of nociceptors found in the oral mucosa.</td>
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<td>• The heat threshold of the oral mucosa was similar to that found in the skin.</td>
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<td>• The threshold for von Frey stimulation was higher in the oral mucosa than in the skin.</td>
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<tr>
<td>• The oral mucosa is richly supplied with both Aδ- and C- innervated polymodal nociceptors.</td>
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*Data from reference (16).
The process of inflammation involves a cascade of events that ensures a rapid physiologic response to tissue injury. Inflammation occurs through the release of a series of chemical mediators. These inflammatory mediators produce pain through direct and indirect effects on nociceptors. The direct effects of inflammatory mediators on nociceptors include activation (i.e., inducing activity in nociceptors) and sensitization (i.e., increasing nociceptor responses evoked by other stimuli) (15).

The inflammatory mediators that directly activate and sensitize primary afferent nociceptors are listed in Table 2. Bradykinin activates primary afferent fibers in vivo (18,19) and produces pain in humans. Serotonin is released from activated platelets and is elevated in inflammatory exudates. It activates primary afferent neurons and results in pain in humans (20–24). Glutamate is an excitatory amino acid that contributes to inflammatory hyperalgesia (25–27) and appears to act through the activation of peripheral N-methyl-D-aspartate receptors. An acidic pH produces pain in normal tissues (28,29) and a pH as low as 5.4 was reported in inflamed tissues (30).

The inflammatory mediators that directly sensitize primary afferent nociceptors include prostaglandins, 8(R),15(S)-dihydroxyeicosatetraenoic acid [8(R),15(S)-diHETE], serotonin, noradrenaline, adenosine, adenosine 5'-triphosphate, nitric oxide, and nerve growth factor (15). Prostaglandins are the best characterized sensitizing agents. During the process of inflammation, they are synthesized from the arachidonic acid that is released from membrane phospholipids. Arachidonic acid is metabolized to prostaglandins by the cyclooxygenase (COX) pathway (31,32). Prostaglandins decrease nociceptive thresholds in behavioral tests in rodents (33,34) and produce tenderness in humans (35).

The lipoxygenase pathway is the second major pathway involved in the sensitization of primary afferent nociceptors. The lipoxygenase pathway converts arachidonic acid into 8(R),15(S)-diHETE. This leukotriene appears to act directly at the receptor of the primary afferent and results in sensitization of the neuron (33,36). In addition to its direct activation effects, serotonin produces hyperalgesia by acting at a different receptor than the receptor involved in activation (37). The catecholamine noradrenaline has been reported to produce hyperalgesia, but only in the presence of tissue injury (38). Adenosine, adenosine 5'-triphosphate, and nitric oxide appear to exert nociceptive effects in inflamed tissue. Nerve growth factor appears to produce sensitization of primary afferent nociceptors by altering their pattern of gene expression of messenger ribonucleic acid encoding a large variety of peptides that alter the excitability of the neuron including bradykinin receptors and sodium channels (15).

As Sonis (17) points out, “a number of clinical observations suggest a physiological complexity in the development of mucositis.” The development of mucositis involves four phases: an inflammatory/vascular phase, an epithelial phase, an ulcerative/bacteriologic phase, and a healing phase (17). Undoubtedly, each of these phases of mucosal injury is associated with some level of pain. The exact mechanisms of pain during each phase of mucosal injury, however, remain to be elucidated. The current article extrapolates information on the nociceptive processes that are known to occur in cutaneous tissues during acute inflammation and suggests that these same processes may be involved in the inflammatory phase of mucosal injury associated with cancer chemotherapy and radiation therapy. Undoubtedly, some of the same inflammatory mediators are involved in producing pain in primary afferents located in the oral mucosa during the initial phase of mucositis. The nociceptive processes that occur during the other phases of mucositis remain to be elucidated not only in the oral mucosa but also in the upper and lower gastrointestinal tract.

**CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH**

Basic and clinical research studies are needed in order to characterize the biology of pain associated with cancer treatment-related mucosal injury. Rigorous longitudinal studies are needed to determine the patterns and severity of pain associated with various stomatotoxic chemotherapy regimens and radiation therapy protocols. Investigations need to characterize the types of pain that occur as a result of mucosal injury not only in the oral cavity but also throughout the entire gastrointestinal tract. The epidemiology of chronic pain and associated side effects should be evaluated in patients who have sustained mucosal injury as a result of cancer chemotherapy or radiation therapy. Finally, the mechanisms of pain experienced during the four phases of mucositis (17) need to be elucidated.

Animal models need to be developed that will allow for an evaluation of the anatomy and physiology of nociceptive pro-
cesses in both normal and inflamed mucosal tissues. Emphasis needs to be placed on determining which inflammatory mediators activate and sensitize primary afferent nociceptors during mucosal injury. Knowledge gained from animal models on the mechanisms of pain associated with mucosal injury can be used to develop and test novel therapies to decrease the pain associated with this major clinical problem.

REFERENCES